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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/315,292	05/20/1999	CLARENCE FRANK BENNETT	ISIS-3561	6344

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EXAMINER	
BOWMAN, AMY HUDSON	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 06/14/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/315,292	BENNETT ET AL.	
	Examiner	Art Unit	
	Amy H. Bowman	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 May 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *66-77* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *66-77* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

5.00

DETAILED ACTION

Status of Application/Amendment/Claims

Applicant's response filed 5/13/2005 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 11/15/2004 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

With entry of the amendment filed on 5/13/2005, claims 66-77 are pending in the application. Applicant has canceled claims 1-65.

New Objections/Rejections

Specification

The disclosure is objected to because of the following informalities: The word "inhalation" is spelled "inihilation" on page 61 of the specification. The word "oligonucleotides" is spelled "oliginucleotides" on page 62 of the specification.

Appropriate correction is required.

Claim Objections

Claims 70 and 71 are objected to because of the following informalities: The word "internucleotide" is spelled "internucelotide" in claim 70. The word

"methylenephosphonate" is spelled "methylenephonphonate" in claim 71. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 67-69 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 67-69 recite the limitation "said 2'-O-substituent" in claim 66. There is insufficient antecedent basis for this limitation in the claim.

Claims 72, 74 and 75 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 72 recites the limitation "wherein said oligonucleotide is an aqueous media. Claim 74 recites the limitation "wherein said oligonucleotide is a saline solution". Claim 75 recites the limitation "wherein said oligonucleotide is a powder". It is unclear how the oligonucleotide itself can be an aqueous media, saline solution, or powder. The claims are being interpreted for purposes of examination to be drawn to an oligonucleotide in such media, rather than being the media.

Claim 76 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. It is unclear what is meant by "suspected to suffer from a disease or disorder". Due to the different possible interpretations of the term "suspected", one would not be able to determine what the metes and bounds of this term is, or what the criteria is for suspecting that a mammal suffers from a disease or disorder.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 76 and 77 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The invention of the above claims is drawn to a method of administering an oligonucleotide into the lung of a mammal known or suspected to suffer from a disease or disorder (asthma, a cancer of the lung, pulmonary fibrosis, rhinovirus, tuberculosis, bronchitis, or pneumonia) which may be diagnosed or treated by said oligonucleotide, comprising aerosolizing the oligonucleotide, and introducing the aerosolized

oligonucleotide into the lung of the mammal, wherein the sugar moiety of at least one nucleoside unit is a 2'-O-substitued nucleoside unit.

Although applicant has shown organ distribution and toxicity *in vivo*, applicant has not shown *in vivo* target inhibition or a resulting treatment effect for the claimed diseases or disorders. The specification does not offer guidance to resolve the known unpredictability in the art associated with appropriate *in vivo* delivery and treatment effects provided by the instantly claimed method. Additionally, applicant has not defined the patient population. One of ordinary skill in the art would not be able to practice the claimed invention without knowing which mammals are suspected to suffer from a disease or disorder which may be treated or diagnosed by the oligonucleotide.

The references cited herein illustrate the state of the art for therapeutic *in vivo* applications using antisense compounds. Branch stresses that "because it is very difficult to predict what portions of an RNA molecule will be accessible in vivo, effective antisense molecules must be found empirically by screening a large number of candidates for their ability to act inside cells" (TIB 23: 45-50 1998). Green et al. states that "[i]t is clear from the evolution of antisense technology from a laboratory research tool into a mechanism for designing active and effective drugs is far from complete. Although there is little doubt that systemically administered antisense [oligonucleotides] can inhibit the expression of specific genes in patients, the effectiveness of such therapy in modifying the course of a particular illness has not yet been established. In addition, toxicity in humans appears more problematic than might be predicted based on preclinical studies in rodents. Clearly, additional work must be done to unravel the

complex problems associated with drug delivery, mRNA targeting and aptameric, nonantisense effects" (Antisense Therapy in Human Disease; Vol. 191, No. 1 2000, pg 103 column 2).

The problems with efficient delivery of antisense oligonucleotides to cells has been addressed by Jen et al., who states that "[o]ne of the major limitations for the therapeutic use of AS-ODNS ...is the problem of delivery.... presently, some success has been achieved in tissue culture, but efficient delivery for *in vivo* animal studies remains questionable (Stem Cells 2000; 18:307-319 pg 315 column 2)." Jen et al. concludes that "[g]iven the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has proven elusive (see p 315, second column)."

As outlined above, it is well known that there is a high level of unpredictability in the antisense art, for therapeutic *in vivo* applications. The scope of the claims in view of the specification as filed together do not reconcile the unpredictability in the art to enable one of skill in the art to make and/or use the claimed invention, namely a therapeutic effect of an antisense oligonucleotide targeted to any given target.

In view of the unpredictability in the art of antisense-based therapy, as outlined above, the specification as filed does not provide adequate guidance that would show how one skilled in the art would practice the claimed invention without undue experimentation. One of skill in the art would be forced to resort to undue trial and error experimentation.

Given the teachings of the specification as discussed above, one skilled in the art could not predict *a priori* whether introduction of any antisense oligonucleotide with a 2'-O-substitued nucleoside unit *in vivo* by the broadly disclosed methodologies of the instantly claimed invention, would result in successful inhibition of expression of a target gene and further result in a treatment effect. To practice the claimed invention, one of skill in the art would have to *de novo* determine; the stability of the particular antisense molecule *in vivo*, delivery of the antisense molecule to the whole organism, specificity to the target tissue *in vivo*, dosage and toxicity *in vivo*, and entry of the molecule into the cell *in vivo* and the effective action therein. Without further guidance, one of skill in the art would have to practice a substantial amount of trial and error experimentation, an amount considered undue and not routine, to practice the instantly claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 66, 72-74, and 76 are rejected under 35 U.S.C. 102(b) as being anticipated by Kole et al.

The invention of the above claims is drawn to a method of administering an oligonucleotide into the lung of a mammal known or suspected to suffer from a disease or disorder which may be diagnosed or treated by said oligonucleotide, comprising aerosolizing the oligonucleotide, and introducing the aerosolized oligonucleotide into the lung of the mammal, wherein the sugar moiety of at least one nucleoside unit is a 2'-O-substitued nucleoside unit. The oligonucleotide is in an aqueous media such as sterilized, pyrogen free water or saline solution.

Kole et al. teach a method of administering an oligonucleotide into a lung of a patient as a therapeutic in the treatment of disease, such as cystic fibrosis, via administering an aerosolized formulation of respirable particles to the lungs (see columns 5 and 6). Kole et al. teach formulations comprising the antisense oligonucleotide comprising sterile aqueous and non-aqueous solutions of the active compound, including saline or water. Kole et al. teach 2'-O-methyl modified oligonucleotides and teach that these modified oligonucleotides are resistant to nucleases and from stable hybrids with RNA that are not degraded by RNase H (see column 8). Therefore, the instant invention is anticipated by Kole et al.

Claims 66-68 and 70-77 are rejected under 35 U.S.C. 102(a) or (e) as being anticipated by Baracchini et al.

The invention of the above claims is drawn to a method of administering an oligonucleotide into the lung of a mammal known or suspected to suffer from a disease or disorder which may be diagnosed or treated by said oligonucleotide, such as asthma, a cancer of the lung, pulmonary fibrosis, rhinovirus, tuberculosis, bronchitis, or pneumonia, comprising aerosolizing the oligonucleotide, and introducing the aerosolized oligonucleotide into the lung of the mammal, wherein the sugar moiety of at least one nucleoside unit is a 2'-O-substitued nucleoside unit. The 2'-O-modification is a 2'-O-alkoxyalkoxy or a 2'-O-methoxyethyl substituent. The oligonucleotide further comprises a phosphorothioate linkage, a 3'-methylenephosphonate, a non-phosphorous containing linkage, a 2'-5' linkage, or is a 3'-deoxy-3'-amino phosphoramidate linkage. The oligonucleotide is in an aqueous media such as sterilized, pyrogen free water or saline solution, or is in a powder.

Baracchini et al. teach antisense oligonucleotide delivery via inhalation or insufflation and formulations including sprays (see column 4). Baracchini et al. teach methods of treating animals suspected of having a condition such as lung cancer comprising administering antisense oligonucleotides (see claims 26 and 29). The methods taught by Baracchini et al. are considered to be as enabled as applicant's instant specification. Additionally, Baracchini et al. teach that oligonucleotides with at least one 2'-methoxyethyl modification are believed to be particularly useful for oral administration (see column 4). Baracchini et al. specifically teach 2'-O-methoxyethyl modifications, 2'alkoxyalkoxy modifications, non-phosphorous containing linkages, as well as phosphorothioate modifications (see columns 6-8). Baracchini et al. teach that

such modifications increase resistance to nucleases. The oligonucleotides taught by Baracchini et al. are administered in aqueous media including sterile water, saline solution, or powders.

Therefore, the instant invention is anticipated by Baracchini et al.

Claims 66-76 are rejected under 35 U.S.C. 102(a) or (e) as being anticipated by Bennett et al.

The invention of the above claims is drawn to a method of administering an oligonucleotide into the lung of a mammal known or suspected to suffer from a disease or disorder which may be diagnosed or treated by said oligonucleotide, comprising aerosolizing the oligonucleotide, and introducing the aerosolized oligonucleotide into the lung of the mammal, wherein the sugar moiety of at least one nucleoside unit is a 2'-O-substitued nucleoside unit. The 2'-O-modification is a 2'-O-alkoxyalkoxy, 2'-O-methoxyethyl, or a 2'-O-dialkylaminooxyalkyl substituent. The oligonucleotide further comprises a phosphorothioate linkage, a 3'-methylenephosphonate, a non-phosphorous containing linkage, a 2'-5' linkage, or is a 3'-deoxy-3'-amino phosphoramidate linkage. The oligonucleotide is in an aqueous media such as sterilized, pyrogen free water or saline solution, or is in a powder.

Bennett et al. teach antisense oligonucleotide delivery via aerosols and formulations including sprays. Bennett et al. teach methods for the treatment and diagnosis of mammalian diseases. The methods taught by Bennett et al. are considered to be as enabled as applicant's instant specification. Bennett et al.

specifically teach 2'-O-methoxyethyl modifications, 2'alkoxyalkoxy modifications, a 2'-O-diakylaminooxyalkyl substituent that is 2'-dimethylaminooxyethoxy in order to enhance the affinity of an antisense oligonucleotide for its target nucleic acid, non-phosphorous containing linkages, as well as phosphorothioate modifications. Bennett et al. teach that such modifications increase resistance to nucleases. The oligonucleotides taught by Bennett et al. are administered in aqueous media including sterile water, saline solution, or powders.

Therefore, the instant invention is anticipated by Bennett et al.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amy H. Bowman whose telephone number is 571-272-0755. The examiner can normally be reached on Mon-Fri 7:00 am – 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Amy H. Bowman
Examiner
Art Unit 1635

JAMES SCHULTZ
PATENT EXAMINER